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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/444,335	11/19/1999	GRIGORI N. ENIKOLOPOV	CSHL99-05	8515

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/444,335	ENIKOLOPOV ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-79* is/are pending in the application.

4a) Of the above claim(s) *25-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24 and 51-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 November 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 7/6/04.

Claims 1-79 are pending. Claims 25-50 were withdrawn from consideration in Paper No. 13, as being drawn to a non-elected invention. Applicant timely traversed the restriction requirement in the response filed 9/11/2000.

Claims 1-24 and 51-79 are under consideration in this Office Action.

This Action is Non-Final due to new grounds of rejection not necessitated by Applicant's amendment.

Drawings

The drawings stand objected to for the reasons indicated in the PTO form 948 accompanying Paper No. 13, issued 10/4/00.

Rejections Withdrawn

The rejection of claims 58-65 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendment.

The rejection of claims 72-78 under 35 USC 103 is withdrawn in favor of a new ground of rejection requiring fewer references. After further consideration, the references were not combined in such a way as to provide adequate motivation to perform measurement of multipotent stem and progenitor cells from a live mammal, or a reasonable expectation of success.

Claim Objections

Claim 4 is objected to because it lacks an article preceding "mouse". Insertion of "a" is suggested.

Claims 5, 13, and 61 are objected to because they lack an article preceding the phrase "rat nestin gene". Insertion of "a" is suggested.

Claims 6, 7, 14, 22, 55, 56, 62, 69, and 75 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 6, 14, 22, 55, 62 and 69 require that the regulatory sequence includes a second intron sequence of the mammalian nestin gene. Claims 7 and 56 require that "the regulatory sequence includes a promoter". However claims from which these claims depend require that "the regulatory sequence includes a nestin promoter and a second intron, or fragment thereof, of the mammalian nestin gene". As such the claims do not further limit the claims from which they depend.

Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 10 requires that the gene encoding the marker fluorescent protein is selectively expressed in multipotent stem and progenitor cells, but claim 9, from

which claim 10 depends, requires that the multipotent stem and progenitor cells must selectively express the marker fluorescent protein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 15, 16, 23, 24, 63, 64, 70, 71, and 76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 15, 16, 23, 24, 63, 64, 70, 71, and 76 are drawn to the genus of regulatory sequences that include a nestin promoter and a second intron, or fragment thereof, of a mammalian nestin gene, **and which further comprise a promoter**. These claims are interpreted as requiring in the regulatory sequence two distinct promoters, i.e. a nestin promoter, and a "further promoter". The specification provides no written support for a regulatory sequence comprising two distinct promoters, and so these claims comprise new matter. Deletion of the claims is suggested.

Scope of Enablement

Claims 1-17, 19-24, and 51, 53-58, 60-66, 68-77, and 79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse, or progeny or embryo thereof, comprising a nucleic acid sequence encoding a marker fluorescent protein operably linked to a regulatory sequence comprising a mammalian nestin promoter and mammalian nestin second intron or second intron fragment, wherein the gene coding for the marker fluorescent protein is selectively expressed in multipotent stem and progenitor cells of the mouse, progeny, or embryo, does not reasonably provide enablement for non-mouse transgenic mammals, progeny, or embryos in which a marker fluorescent protein is expressed in multipotent stem and progenitor cells of the non-mouse mammal, progeny or embryo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claimed invention encompasses a nonhuman transgenic mammal or mouse, progeny, or embryo thereof, comprising a nucleic acid sequence encoding a marker fluorescent protein operably linked to a regulatory sequence comprising a mammalian nestin promoter and second intron wherein the gene coding for the marker fluorescent protein is expressed in multipotent stem and progenitor cells of the mammal, progeny, or embryo. Although independent claims 1, 9, 19, 51, 58, 66, 72, and 79 require expression in multipotent stem and progenitor cells of the mammal or mouse, only certain dependent claims (2, 10,

20, 52, 59, 67, and 73) require selective expression in those cells. As such, the broader claims are not limited in terms of the other types of cells in which the marker is expressed, and may be interpreted as embracing animals in which all cells express the marker protein. This type of result could occur if, for example, the transgene construct integrated downstream of the promoter of a house keeping gene and expression of the transgene was subsequently influenced by the house keeping gene promoter.

The specification teaches that the claimed animal may be used to facilitate isolation or detection of multipotent stem and precursor cells. It follows that in order to function as intended, the marker protein should be expressed selectively in multipotent stem and progenitor cells of the mammal, rather than in a large proportion of cells or in all cells. If the marker is expressed non-selectively, then one cannot take advantage of the fluorescence to identify or isolate multi-potent stem and precursor cells. The specification does not teach how to use the scope of claimed mammals in which expression of the marker does not occur selectively in multipotent stem and progenitor cells, and one of skill in the art would have to perform undue experimentation in order to use these animals as intended in the specification.

Claims 1-24, 72-77, and 79 embrace non human transgenic mammals that express a fluorescent marker protein in multipotent stem and progenitor cells, whereas the specification exemplifies a transgenic mouse which selective express a fluorescent marker protein in such cells. With regard to the scope of transgenic mammals embraced by the claims, it is well known in the art that the

production of transgenic animals with desired characteristics is highly unpredictable. As of the effective filing date of the claimed invention only a limited number of species of transgenic animals had been produced. There is no evidence which supports that transgenic animals from all species possessing the desired phenotype can be readily produced without undue experimentation. It is also well known in the art that the expression of a transgene and the effects of its expression on the animal as a whole are not predictable due to numerous uncontrollable factors such as the site of integration and methylation-inactivation of the transgene. See Kappel et al, right column of page 549, for example. With respect to the DNA construct required to make the animals, the specification is not enabling for the use of all combinations of mammalian nestin regulatory sequences and fluorescent proteins. It is well known in the art that the level and the specificity of expression of a transgene as well as the phenotype of the transgenic animal thus produced are greatly dependent of the specific transgene construct used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are all important factors in controlling the expression of a transgene.

Wall (Theriogenology, 1996) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements and may result in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). The nature of the chromatin at the site of insertion can control the expression of the transgene with respect to developmental timing, tissue specificity, and frequency of transcription initiation.

These position effects vary with the site of integration, which is totally unpredictable. Additionally, Kappel et al (Current Opinion in Biotechnology, 19.92) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). The level of skill in the transgenic art is such that one cannot predict whether a transgene that is expressed in a mouse will also be expressed efficiently in another animal. Mullins teaches that position effects can cause loss of cell specificity of expression, overexpression, or silencing of the transgene, and that a given construct may react very differently from one animal to another. See page S37, lines 7-12, and page S39, first sentence of first paragraph. Furthermore, Ebert et al. (Molecular Endocrinology, (1988) disclose the production of transgenic mice expressing human somatotropin regulated by the mouse metallothionein promoter at levels sufficient to cause an increase in growth; however, expression of the same transgene in pigs did not produce pigs exhibiting the same phenotypic result (page 277, Introduction, column 2).

Hammer et al (Journal of Animal Science, 1986), disclose the production of transgenic mice, sheep and pigs; however only mice exhibited an increase in growth due to the expression of human growth hormone (pages 276-277, Subsection: (Effect of Foreign GH on Growth). Thus, with respect to the unpredictability of transgene expression levels sufficient to confer a particular phenotype due to species differences and/or specific elements within a transgene construct, it would have required an undue amount of experimentation

to extend the results obtained in mice to levels of transgene product in other non-human transgenic mammals expressing transgenes encoding fluorescent marker proteins I the appropriate cells, and therefore, the required phenotype.

The specification teaches a working example in which the rat nestin promoter and second intron are used to drive expression of green fluorescent protein (GFP) in transgenic mice, and cells are isolated and quantified by fluorescence activated cell sorting. The specification does not reduce to practice any other expression constructs and does not disclose a working example of any other transgenic mammal. The specification teaches that the number, size, and shape of fluorescent cells may be measured, as well as the intensity of their fluorescence which is indicative of gene expression. Additionally, fluorescence of the cells may be used to monitor neural stem and progenitor cells in vivo in order to follow the effects of various drugs and differentiating agents administered in vivo or in vitro, to investigate neurogenesis in the normal brain during both embryonic and post embryonic stages, after brain injury or after transplantation experiments. Cell migration during normal organ development may also be measured.

The prior art teaches transgenic mice comprising reporter genes linked to rat or human nestin promoters and corresponding second introns, wherein beta galactosidase is expressed in neural progenitor cells. See Zimmerman et al (1994), or Lothian et al (Eur. J. Neurosci. 9 :452-462, 1997). The second intron is considered to be evolutionarily conserved, and the rat and human sequences are highly homologous with many recognized transcription factor binding sites.

See Lothian (1997) and Lothian et al (Exp. Cell Res. 248:509-519, 1999). Yamaguchi et al (Neuroscience Research Supplement 22: S286, (1998) taught a transgenic mouse comprising GFP operably linked to a nestin promoter, but was silent as to the presence or absence of introns. Neuronal stem cells could be easily visualized in vivo in the mice. The prior art teaches no example of a non-mouse transgenic mammal comprising a transgene driven by a nestin promoter and second intron.

In view of the state and unpredictability of the prior art as discussed above, the lack of non-mouse working examples or guidance as to how to overcome the art recognized unpredictability, in the specification does not provide sufficient guidance on how to produce transgenic mammals, other than mice, with the desired phenotype and utility.

Claims 19-24 and 72-77 embrace methods of measuring multipotent stem and progenitor cells in a live animal, organ, or tissue of the live animal, by measuring fluorescence of cells from a live non-human transgenic mammal. While the preamble embraces the scope of all animals, the method steps require use of mammals. Should Applicant overcome the portion of this rejection limiting the enabled scope of animals to mice, claims 19-24 and 72-78 would still lack enablement because the specification fails to teach how to use transgenic mammals expressing GFP in multipotent precursor or stem cells to measure any population of cells in a non-mammal. This scope of embodiments is clearly inoperative and would require undue experimentation.

Response to Arguments.

Please note that the portion of the foregoing rejection dealing with the enabled scope of transgenic mammals was originally given in the first action on the merits, mailed 10/4/2000. The rejection was withdrawn in the following final rejection mailed 6/20/2001. After further consideration, it was determined that the rejection was withdrawn erroneously. Applicant's arguments against the rejection, filed 4/9/01, have been completely considered below, but are unpersuasive.

Applicant responds to the rejection at pages 9-13 of the response. Arguments at pages 9-11 and 13 are directed to whether or not transgenic mammals can be made. The Office does not dispute that transgenic mammals can be made. The issue is whether or not one can obtain a desired phenotype, such as transgene expression in a specific subset of cells i.e. multipotent stem and progenitor cells. At page 11, paragraph 4, Applicant argues that expression of a transgene in a specific subset of cells, as claimed, is not a phenotypic trait. This argument is unpersuasive because it is only an opinion and lacks any evidentiary or logical support. The Merriam Webster's Collegiate Dictionary (10^{th} edition, Merriam-Webster, Inc. Springfield, MA) defines phenotype as the visible properties of an organism that are produced by the interaction of the genotype and the environment. See page 872. Clearly the interaction of transgenic cells with excitatory light to produce fluorescence meets this definition.

At page 12, first and second paragraphs, Applicant continues to argue that one of skill in the art can produce transgenic mammals. As stated above, the

Office recognizes that transgenic mammals can be produced but that their phenotype is unpredictable. At paragraph 3 of page 12, Applicant argues that Mullins teaches that position effects that contribute to unpredictability can be overcome by incorporating a number of elements that function across species barriers, such as large amounts of flanking sequences. Examination of the passage referred to in Mullins shows that these procedures are referred to as *possible* solutions that *may* be sufficient to overcome some problems. It is clear from the paragraph in question that position effects can have direct effects on the cell specificity of transgene expression, and that the solutions proposed by Mullins may, or may not, overcome these problems. Furthermore, position effects are only one of several problems that lead to unpredictability of phenotype including CpG methylation, and appropriate recognition of expression control elements by the right transcription factors at the right developmental time.

At page 12, last paragraph Applicant argues that Ebert teaches that major phenotypic changes can be produced in transgenic livestock. Again, this is not the issue. The issue is whether or not one can reproducibly and predictably obtain the same phenotype in different transgenic animals. The prior art teaches that one cannot. For these reasons the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16, 24, 64, and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16, 24, 64, and 71 are indefinite because they recite "the promoter" without antecedent basis. There are two antecedents for "the promoter", i.e. the nestin promoter, and the "further promoter".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-14, 17, 19-22, 51-62, 65-69, 78 and 79 stand rejected under 35 U.S.C. 102(b) as being anticipated by Zimmerman (1994) as evidenced by Hogan (1986).

Zimmerman teaches transgenic mice comprising a lac-Z transgene under the control of the promoter and second intron enhancer of the rat nestin gene. Beta galactosidase was expressed in neuronal stem cells of the resulting animals, and allowed measurement of these cells. See entire document, especially Abstract; Table I, pages 12, 13, particularly constructs B, C, and F; Fig. 2 on page 15; and page 23, fourth full paragraph. It is noted that beta galactosidase comprises 38 tryptophan residues and is therefore a fluorescent

protein, and cells which comprise it have the property of fluorescence. The mice were made by the method of Hogan, i.e. by coinjection of recombinant expression constructs into the pronuclei of fertilized mouse eggs. See sentence bridging pages 153 and 154; and pages 157-173 of Hogan. With regard to claim 79, requiring adult mice, Zimmerman taught mice of breeding age. See e.g. page 14, lines 3-7.

It is noted that a similar rejection was previously withdrawn in the Final Rejection mailed 10/7/2002 in view of Applicant's amendments requiring that "the expression of the gene encoding the marker fluorescent protein is detected using fluorescence." After further consideration it was determined that withdrawal of the rejection was erroneous. MPEP 2173.05(g) requires that a functional limitation must be evaluated for what it fairly conveys to a person of ordinary skill in the pertinent art. One of ordinary skill in the art could clearly detect beta galactosidase by either its own fluorescence (e.g. by purifying it from cells of the animal and quantitating it by fluorescence spectroscopy), by detection of fluorescently labeled anti-beta galactosidase antibodies bound to beta galactosidase in situ, or by detection of fluorescent reaction products (note that the claim does not require measurement of the fluorescence of the marker protein per se, it requires only detection of fluorescence, broadly).

Thus Zimmerman anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-15, 17, 18-22, 24, 51-63, 65-69, 78, and 79 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman (1994) in view of Chiochetti (1997).

Zimmerman teaches transgenic mice comprising a construct containing a lac Z reporter transgene under the control of the promoter and second intron enhancer of the rat nestin gene. Beta galactosidase was expressed in neuronal stem cells of the resulting animals, and allowed measurement of these cells. See entire document, especially Abstract; Table I, pages 12, 13, particularly constructs B, C, and F; Fig. 2 on page 15; and page 23, fourth full paragraph. With regard to claim 79, requiring adult mice, Zimmerman taught mice of breeding age. See e.g. page 14, lines 3-7.

Zimmerman does not teach a construct comprising green fluorescent protein.

Chiochetti teaches that green fluorescent protein (GFP) is a more powerful and sensitive tool for studying gene expression in transgenic animals than is beta galactosidase. GFP fluorescence easily identified a greater number of positive cells than beta galactosidase, and the pattern generated by GFP more closely

matched the endogenous gene expression as measured by in situ hybridization. See entire document, especially abstract; sentence bridging pages 193 and 194; page 199, column 1, first two full paragraphs; page 202, column 1, lines 5-7.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Zimmerman by substituting green fluorescent protein for beta galactosidase, and to study gene expression in neuronal stem cells in living animals and their organs and tissues. One would have been motivated to do so because Chiochetti teaches that green fluorescent protein (GFP) is a more powerful and sensitive tool for studying gene expression in transgenic animals than is beta galactosidase.

Thus the invention as a whole was *prima facie* obvious.

Claims 1-15, 17-22, 24, 51-63, 65-69, 72-75, and 77- 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman (1994) in view of Yamaguchi et al (Neuroscience Research Supplement 22: S286, (1998).

Zimmerman teaches transgenic mice comprising a construct containing a lac Z reporter transgene under the control of the promoter and second intron enhancer of the rat nestin gene. Beta galactosidase was expressed in neuronal stem cells of the resulting animals, and allowed measurement of these cells. See entire document, especially Abstract; Table I, pages 12, 13, particularly constructs B, C, and F; Fig. 2 on page 15; and page 23, fourth full paragraph. With regard to claim 79, requiring adult mice, Zimmerman taught mice of breeding age. See e.g. page 14, lines 3-7.

Zimmerman does not teach a construct comprising green fluorescent protein.

Yamaguchi taught adult transgenic mice comprising a GFP gene under the control of a nestin promoter. Neuronal stem cells could be easily visualized in vivo in the mice. Yamaguchi was silent as to the nature of the regulatory control regions present in the promoter. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Zimmerman by substituting green fluorescent protein for beta galactosidase, and to study gene expression in neuronal stem cells in living animals and their organs and tissues. One would have been motivated to do so because Yamaguchi teaches that GFP allows visualization of neuronal stem cells in vivo, and that study of such cells in vivo would lead to an understanding of the process of organization and plastic changes of the neuronal circuit during development and in adults. See abstract

Response to Arguments

Applicant's arguments, filed 7/6/04 have been fully considered as they apply to the rejections above, but they are not persuasive.

With regard to the rejection under 35 USC 102, Applicant argues that beta galactosidase is not a marker fluorescent protein. Applicant asserts that the term "marker fluorescent proteins" means a special group of proteins to a skilled person in the art, and that beta galactosidase is not a marker fluorescent protein because its fluorescence is not strong enough for the protein to be useful as a marker fluorescent protein. This argument is unpersuasive because it is only a statement of opinion and lacks evidentiary support. A search of the prior art for the term "marker fluorescent protein" using 74 databases available to the PTO, including MEDLINE, CAPLUS, and USPATFULL, returned no hits. This is objective evidence that, at the time the invention was filed, "marker fluorescent protein" was not a recognized term of art, and that Applicant's argument is only an unsupported statement of opinion. Applicant has presented no evidence to the contrary, and no evidence that beta galactosidase is not fluorescent, or that it cannot be used as a marker by virtue of its inherent fluorescence, the fluorescence of antibodies that recognize it, or the fluorescence of its reaction products. Note that the claims do not require measurement of the fluorescence of the marker protein.

With regard to the rejections under 35 USC 103, Applicant argues that a skilled artisan would not have expected that the level of expression obtained in the claimed animal would allow real-time, whole body imaging of a live mammal. Applicant states that the cited art does not suggest that GFP's expression is strong enough to allow for real-time whole body imaging.

This argument is unpersuasive because it lacks any evidentiary support. The only support for this position is the declaration of Dr Hoffmann, filed 8/6/02, which is a statement of opinion. This declaration does not provide evidence of unexpected results that overcomes the obviousness rejections. MPEP 716.02(b) discusses the burden on Applicant in overcoming an obviousness rejection by presentation of evidence of unexpected results. "The evidence relied up [sic] should establish "that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance." Ex parte Gelles, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). In this case, it has not been established that the obtained results are statistically or practically different from those of the prior art. It was known in the prior art that the nestin promoter was an effective promoter for expression of beta galactosidase in transgenic animals (Zimmerman, 1994). It is clear that there is motivation to substitute GFP for beta galactosidase (See, Chiochetti 1997). Absent evidence to the contrary, one of ordinary skill in the art could reasonably expect a similar level of GFP expression as was obtained for beta galactosidase. Applicant has provided no evidence that GFP would be expressed at any unexpectedly greater level than was beta galactosidase, i.e. Applicant has presented no evidence that the level of GFP expression obtained was unexpected. Because the fluorescence intensity is directly related to the quantity of GFP produced, there is no reason of record to expect any less fluorescence than that which was observed by Applicant.

Even if evidence had been presented to show that one of skill in the art would not have expected to be able to perform real-time whole body imaging on the GFP-mammal, MPEP 716.02(a)(III) indicates that the submission of evidence that a new product possesses unexpected properties does not necessarily require a conclusion that the claimed invention is nonobvious, citing *In re Payne*, 606 F.2d 303, 203 USPQ 245 (CCPA 1979), and referring to the discussion of latent properties and additional advantages in MPEP § 2145. MPEP 2145 states that mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention, citing *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). "The fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious." *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985) (The prior art taught combustion fluid analyzers which used labyrinth heaters to maintain the samples at a uniform temperature. Although appellant showed an unexpectedly shorter response time was obtained when a labyrinth heater was employed, the Board held this advantage would flow naturally from following the suggestion of the prior art). It follows that, contrary to Applicant's assertion, the relevant issue is the level of expected GFP expression that would have been expected in the prior art, not the issue of whether or not one might recognize a new use for an obvious product. In the absence of evidence that the product suggested by the prior art was somehow different form the claimed product, the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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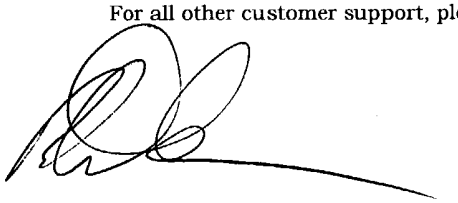

Richard Schnizer, Ph.D.